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(54) Title: TECHNIQUE FOR MANIPULATING MEDICAL IMAGES

(57) Abstract: The invention and the embodiments described in this invention provide new techniques for manipulating digital images and is particularly useful for extracting tissues (i.e., assigning tissue boundary locations) from medical images. These techniques can be applied to diagnosing arthritis and for monitoring disease progression or response to therapeutic intervention. The invention provides for means to extract the articular cartilage from medical images for analysis purposes.

TECHNIQUE FOR MANIPULATING MEDICAL IMAGES

BACKGROUND OF THE INVENTION

MR imaging is currently the most accurate technique for assessing the articular cartilage non-invasively in vivo. A large array of different pulse sequences can be used for imaging articular cartilage. However, at present, the diagnosis of cartilage loss is based mostly on qualitative, visual analysis by the radiologist. One of the major obstacles in evaluating patients with osteoarthritis has been the lack of accurate and reproducible quantitative image processing and analysis techniques for monitoring progression of cartilage loss and response to medical or surgical therapy.

Some investigators reported the use of three-dimensional reconstruction of the articular cartilage with subsequent volumetric quantification of the entire cartilage surface. In one study, cartilage was segmented from the surrounding tissues using a signal intensity based thresholding technique applied to magnetization transfer subtraction images or fat-saturated T1-weighted images [1]. Since some of the adjacent tissues demonstrated signal intensity values overlapping those of articular cartilage, additional manual disarticulation of the cartilage was performed on selected image slices. Knees were imaged repeatedly. Cartilage volumes determined from the 3D reconstructions of MT subtraction and T1-weighted fat-saturated images were correlated to values obtained with water displacement of surgically retrieved tissue. They reported an intra-observer reproducibility error of 0.20-0.65 mL (3.6%-6.4%) for MT subtraction imaging and 0.21-0.58 mL (4.2%-6.4%) for T1-weighted fat-saturated imaging [1]. Interobserver error was less than 0.62 mL and 7.8%. In a subsequent study involving the metacarpophalangeal joints, they found a reproducibility error of 5.2% (95% confidence interval 2.9% to 7.6%) for metacarpal cartilage and 9.9% (5.4% to 15.1%) for proximal phalangeal cartilage [2]. They concluded that three-dimensional data analysis of MR images allows reproducible volumetric quantification of articular cartilage in the knee and metacarpophalangeal joints.

Piplani et al. refined this approach by combining signal intensity based thresholding of the articular cartilage with a connected-components or seed growing algorithm thereby obviating the need for manual disarticulation of the cartilage in those areas where adjacent tissues demonstrated overlapping signal intensities [3].

Stammberger et al. used B-spline snakes for semi-automated segmentation of articular cartilage [4]. A continuous and smooth parametric curve that depends on a number of control points is fit around the object by means of minimizing different energy terms. These energy terms control the smoothness of the curve and its attraction to certain image features, e.g. high graylevel gradients, causing it to act much like a rubber band.

Lynch et al. demonstrated a variation of the snake algorithm, in which the spline is adjusted to minimize costs calculated from Gauss and Canny filter responses [5]. The user initializes the system by selecting different control points in the medial and lateral tibio-femoral and the patello-femoral compartments. These control points are subsequently automatically adjusted as far as possible.

However, at present, there are no techniques available that perform reliably when used for segmentation of cartilage affected by advanced osteoarthritis. In these cases, MR images typically show a high degree of texture inhomogeneity of the cartilage, irregular and interrupted contours, and low contrast between the cartilage and surrounding tissue. These situations require a different technique for segmentation of the cartilage.

We developed a system for the calculation of the 3-dimensional cartilage thickness that is based on a 3D Euclidian distance transformation (EDT). For a given set of feature points in a binary volume, the EDT computes the distance to the closest feature point for each non-feature point of the volume. By using the points on the cartilage-bone interface (inner cartilage surface, ICS) as feature points, the EDT measures the distance to the closest voxel on the ICS for all other points, including the ones on the outer cartilage surface (OCS), resulting in a truly three-dimensional distance value determined normal to the ICS (Fig. 1).

SUMMARY OF THE INVENTION

The general purpose of the invention and the embodiments described in this invention is to provide new techniques for extracting tissues from medical images. These techniques can be applied to diagnosing arthritis and for monitoring disease progression or response to therapeutic intervention.

In one embodiment, the invention provides for means to estimate the volume of cartilage layers in articular joints such as the knee joint using magnetic resonance imaging (MRI) scans. In another embodiment, the invention provides for means to estimate the thickness distribution of articular cartilage layers using an MRI scan. In another

embodiment, the invention provides for means to measure volume and thickness distribution of specific volumes of interest (VOIs) in an MRI scan. In another embodiment, the invention provides for means to compare baseline and follow-up MRI scans of a patient. In another embodiment, the invention provides for means to identify the articular cartilage in an image, such as an MRI. In another embodiment, the invention provides for means to extract the articular cartilage from medical images for analysis purposes.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 demonstrates a 2D MRI (3D spoiled gradient echo. The 2D MRI demonstrates a full thickness cartilage defect in the posterior lateral femoral condyle (arrows), as well as texture inhomogeneity

Figure 2 demonstrates the distance d between the inner cartilage surface (ICS) and the outer cartilage surface (OCS), as used, for example, for the new live wire feature.

Figure 3 shows a schematic of the use of an aspect of the invention, in this example used with the Live Wire algorithm. A. low contrast between OCS and surrounding tissue; bel b has low cost since gradients $\vec{\beta}$ and $\vec{\gamma}$ are almost parallel. B. High contrast between OCS and surrounding tissue; b has low cost due to high magnitude of gradient $\vec{\beta}$.

Figure 4 shows a schematic of bel b and its neighborhood of pixels p, q, t, u, v, w.

PREFERRED EMBODIMENTS

In one embodiment the invention provides for a method of manipulating an image which method comprises extracting a tissue from said image wherein said extraction is facilitated with use of knowledge of the thickness, curvature, shape, dimensions or contour of said tissue. The tissue that can be extracted in the fashion can be bone or cartilage.

In another embodiment of the invention, knowledge of the thickness, curvature, shape, dimensions or contour of said tissue can be obtained from other subjects. These subjects can be age and sex matched with the patient. These subjects can be weight matched. These subjects can also have similar medical histories, for example a tear of the anterior cruciate ligament.

In another embodiment of the invention, knowledge of the thickness, curvature, shape, dimensions or contour of said tissue can be obtained from a reference database. This reference database can have bee generated in other age, sex, weight, or race matched

individuals. Individuals can also have similar medical histories, for example a tear of the medial meniscus.

In another embodiment of the invention, knowledge of the thickness, curvature, shape, dimensions or contour of said tissue can be obtained from information derived from the same subject. For example, in segmenting arthritic or normal cartilage in a medical image, said information can be cartilage thickness, cartilage curvature or cartilage shape in a contralateral joint. Alternatively, said information on cartilage thickness, cartilage curvature or cartilage shape can be obtained in the same joint.

In another embodiment, the thickness, curvature, shape, dimensions or contour of another tissue, preferably a tissue adjacent to the tissue of interest, can be used to facilitate the segmentation or extraction of the tissue of interest. For example, in segmenting arthritic or normal cartilage in a medical image, the shape or contour of the subchondral bone can provide an estimate of the expected contour of the articular cartilage.

In another embodiment of the invention, knowledge of the thickness, curvature, shape, dimensions or contour of said tissue can be used to verify plausibility and correctness of the manipulation or segmentation of said tissue. For example, in segmenting normal cartilage in a medical image, a cartilage thickness or dimensions calculated from the segmentation that far exceed reference values from other patients matched by weight and height or values calculated from a baseline exam are likely to be incorrect.

In another embodiment, 2D MRI images can be used to create a 3D map of the articular cartilage thickness using (for example) color coding to map thickness on a pixel-by-pixel basis. This can be displayed, for example, along the 3D surface of the articular cartilage.

This invention can be applied to any joint in a human or mammal, for example a knee joint or a hip joint. This invention can be particularly useful in humans suffering from arthritis and cartilage loss.

Another aspect of the invention is a method for assessing the condition of cartilage in a joint of a human, which method comprises

(a) electronically transferring an electronically-generated image of a cartilage of the joint from a transferring device to a receiving device located distant from the transferring device;

(b) receiving the transferred image at the distant location;

(c) extracting said cartilage from said transferred image

(d) converting the transferred image to a normal or degeneration pattern of the cartilage;

(e) storing said normal or degeneration pattern of cartilage in a database, and

(f) transmitting said normal or said degeneration pattern to a site for analysis.

The information stored in the database on said normal and degeneration patterns can be used to facilitate said extraction of cartilage from said transferred images in other patients or to verify plausibility and correctness of said extraction of cartilage from said transferred images in other patients.

Another aspect of the invention is a method for assessing the condition of cartilage in a joint of a human, which method comprises

(a) extracting said cartilage from said image

(b) electronically transferring an electronically-generated image of said extracted cartilage of the joint from a transferring device to a receiving device located distant from the transferring device;

(c) receiving the transferred image at the distant location;

(d) converting the transferred image to a normal or degeneration pattern of the cartilage;

(e) storing said normal or degeneration pattern of cartilage in a database, and

(f) transmitting said normal or said degeneration pattern to a site for analysis.

The information stored in the database on said normal and degeneration patterns can be used to facilitate said extraction of cartilage from said transferred images in other patients or to verify plausibility and correctness of said extraction of cartilage from said transferred images in other patients.

The live wire algorithm that was introduced by Falcão et al. [6] can provide a flexible general framework well-suited for adaptation for the purpose of segmenting osteoarthritic cartilage. It can evaluate different features of the oriented edges between two pixels (boundary element, *bel*) and finally can calculate a single cost value for every bel based on these features. For a starting pixel P that is selected by the user with the mouse, the system can calculate the bel path with the least sum of costs from each image pixel to P. When the user moves the mouse cursor, the system can now draw the calculated path from the current mouse position. The current path can be frozen as part of the object contour by the user. Thus, the object contour is assembled from a number of live wire segments.

The live wire algorithm as presented by Falcão et al. is, however, too general to be effective in the segmentation of osteoarthritic cartilage. The current invention can be used to enhance and extend the live wire algorithm, thus providing for means to efficiently segment cartilage from MR images in patients with severe osteoarthritis.

In one embodiment of the invention, a live wire technique can be used to segment the cartilage. Various features can be used alone or in combination to help segment the articular cartilage with the live wire technique. Such features include, but are not limited to:

1. Grayvalue of the pixel on the left side of the bel
2. Grayvalue of the pixel on the right side of the bel
3. Magnitude of the graylevel gradient across the bel
4. Distance of the closest bel in the previously segmented slice

For example, the distance of the outer cartilage surface (OCS) to the inner cartilage surface (ICS) can be used as an aid in segmenting the cartilage.

Prior knowledge that femoral cartilage, for example, usually does not exceed a thickness of approximately 4 mm can be used with this feature. If the cartilage-bone interface (ICS) is segmented first in a slice, which can usually be easily done on sagittal MR images due to high contrast between bone and cartilage, this information can be helpful in regions of low contrast between OCS and surrounding tissue. The feature value is the distance of the bel to the closest bel on the ICS (see Fig. 2). For distance calculation, a Euclidean distance transform algorithm can be used. The cost can be calculated with a modified hyperbolic function that increases from 0 to 1 above a thickness value taken from a reference database. This feature can prevent the OCS contour from moving too far away from the ICS contour.

In another embodiment of the invention, the direction of the graylevel gradient of the OCS compared with the gradient of the corresponding section of the ICS can be used to help in segmenting the cartilage.

Except in the periphery of the cartilage where the ICS and the OCS meet and in regions of defective cartilage the OCS is usually approximately parallel to the ICS. This knowledge can be used to combine magnitude and direction of the graylevel gradient in order to help finding the contour in regions of low contrast between the OCS and surrounding tissue. If b is a boundary element under consideration for the OCS and c the closest bel on the previously segmented ICS, and $\vec{\beta}$ and $\vec{\gamma}$ are the vectors of the graylevel gradient across b and c, the value f for this feature can be computed as follows:

$$f = \frac{1}{|\vec{\beta}|} \cdot \left(1 - \left| \frac{\vec{\beta} \cdot \vec{\gamma}}{|\vec{\beta}| \cdot |\vec{\gamma}|} \right| \right) \qquad (1)$$

In this equation, the first factor is the inverse of the gradient magnitude across *b*. The second factor includes the absolute value of the cosine of the angle ψ between $\vec{\beta}$ and $\vec{\gamma}$ and has a low value when the vectors are nearly parallel since $|\cos\psi|$ is close to 1. Thus, the lower the gradient magnitude across *b*, the more weight is given to its direction. The cost function is a linear mapping within a predetermined interval I of feature values. Values outside of I are mapped to 1.

Thus, within I the cost for *b* increases with increasing deviation of the direction of gradient $\vec{\beta}$ from the direction of the gradient on the opposing ICS. A high degree of parallelism between $\vec{\beta}$ and $\vec{\gamma}$ results in a high probability of *b* being included in the contour (see Fig. 3A). In effect, this means that the ICS is taken as a template for the OCS where the OCS is not clearly recognizable. In areas of high contrast between the OCS and surrounding tissue, however, this is not necessary, so that the gradient direction can be weighted less (see Fig. 3B). This also makes the detection of cartilage defects possible.

In another embodiment, different boundary element features may be considered together. Their relative weighting can be the same for each slice or can be changed depending on regional variations in one or more of these features.

The invention provides for means to reliably segment articular cartilage from MR images that has been damaged due to advanced osteoarthritis. In one embodiment, the invention will be used to determine the total volume of an articular cartilage layer.

In another embodiment, the invention will be used to calculate the 3-dimensional thickness distribution of an articular cartilage layer.

In another embodiment, the invention will be used to calculate a volume of interest that is targeted over an area of diseased cartilage rather than including the entire surface of the articular cartilage.

In another embodiment, the invention provides for means to compare baseline and follow-up studies of a patient. This will be done by segmenting the articular cartilage in both studies using the invention, and subsequently registering the segmented cartilage objects by means of a surface registration technique.

In another embodiment, the invention provides means to verify plausibility and correctness of said thickness and volume calculations.

The techniques provided in this invention provide means to accurately and reliably extract cartilage from medical images. For example, the techniques described in this invention provide means to accurately and reliably segment cartilage from MR scans that has been destroyed or deformed due to osteoarthritis. Existing cartilage segmentation methods do not perform reliably and accurately in case of diseased cartilage. The invention improves the diagnostic capabilities of cartilage quantification methods that can be used for the assessment of arthritis, for example in patients undergoing treatment with a chondroprotective or a chondroregenerative agent. The invention also facilitates the segmentation process for the user, thus reducing the amount of time necessary to segment cartilage from the MR or other medical images.

Someone skilled in the art will easily recognize other means of practicing the invention. For example, the specific cost mapping functions used to calculate the feature costs, and its parameters can be easily modified. Variations of formula 1, leading to similar results, are evident.

EXAMPLES

The examples below are exemplary of how aspects of the invention can be practiced. The examples are in no way meant to be limiting of the invention. Someone skilled in the art will easily recognize other means of practicing the invention.

In one example, a live wire algorithm is used for segmentation of osteoarthritic cartilage. Several features can be used alone or in combination to help segment the articular cartilage with the live wire technique. The features in this example include:

1. the grayvalue of the pixel on the left side of the bel
2. the grayvalue of the pixel on the right side of the bel
3. the magnitude of the graylevel gradient across the bel
4. the distance of the closest bel in the previously segmented slice
5. the distance of the outer cartilage surface (OCS) to the inner cartilage surface (ICS).

Prior knowledge that femoral cartilage, for example, usually does not exceed a thickness of approximately 4 mm can be used with this feature. The feature value is the distance of the bel to the closest bel on the ICS (see Fig. 2). For distance calculation, a Euclidean distance transform algorithm can be used. The cost is calculated with a modified

hyperbolic function that increases from 0 to 1 above a reference thickness value. This feature can prevent the OCS contour from moving too far away from the ICS contour.

Listing of preferred embodiments of the invention

As will be apparent to those of skill in the arts to which the current invention pertains, there are numerous elements involved in the practice of the invention, and those elements can be combined in different manners to provide multiple embodiments of the invention. A non-exhaustive list of preferred embodiments is provided to exemplify practice of the invention. This list is primarily directed to medical applications, particularly those that relate to the determination of the outer cartlidge surface of an articular joint, as determination of such a surface from a digital image is a particularly difficult challenge for which the present invention is well suited.

1. A method of manipulating an image which method comprises

   a. determining the gray value of a pixel on the left side of a boundary element

   b. determining the gray value of a pixel on the right side of a boundary element

   c. determining the magnitude of the graylevel gradient across the boundary element

   d. determining the distance of the closest boundary element in the previously manipulated image slice,

whereby determining the distance of the closest boundary element in the previously manipulated image slice improves the accuracy of the manipulation.

2. The method of embodiment 1 wherein the image is an MRI and the method is used to locate the bone cartilage interface.

3. The method of embodiment 1 wherein the image is an MRI and the method is used to locate the external cartilage surface.

4. The method of embodiments 2 and 3 wherein the cartilage is normal.

5. The method of embodiments 2 and 3 wherein the cartilage is diseased.

6. A method of manipulating an image which method comprises extracting a tissue from the image wherein the extraction is facilitated with use of knowledge of the thickness, curvature, shape or contour of the tissue.

7. The method of embodiment 6 wherein the tissue is bone.

8. The method of embodiment 6 wherein the tissue is cartilage.

9. The method of embodiment 6 wherein the knowledge of the thickness, the curvature, or the contour is obtained from information derived from other subjects.

10. The method of embodiment 9 wherein the other subjects are age and sex matched with the patient.

11. The method of embodiment 9 wherein the other subjects are weight matched.

12. The method of embodiment 6 wherein the knowledge is obtained from information derived from the same subject.

13. The method of embodiment 6 wherein the information is cartilage thickness, cartilage curvature or cartilage shape in a contralateral joint.

14. The method of embodiment 6 wherein the information is cartilage thickness, cartilage curvature or cartilage shape in the same joint.

15. The method of embodiment 6 wherein the knowledge is curvature or shape of the bone in the same joint.

16. The method of embodiment 15 wherein the bone is subchondral bone.

17. The method of embodiment 16 wherein the curvature or the shape of the subchondral bone is used to estimate the curvature or shape of the overlying articular cartilage.

18. The method of embodiment 6 wherein the image is an image of the knee joint.

19. The method of embodiment 18 wherein the joint has arthritis.

20. The method of embodiment 19 wherein the arthritis has caused cartilage loss.

21. A method of manipulating an image which method comprises segmenting the image wherein the segmentation is facilitated with use of knowledge of an expected range of the thickness, curvature, shape, dimensions or contour of at least one tissue.

22. The method of embodiment 21 wherein the tissue is bone.

23. The method of embodiment 21 wherein the tissue is cartilage.

24. The method of embodiment 21 wherein the knowledge of the thickness, the curvature, the shape, the dimensions or the contour is obtained from information derived from other subjects.

25. The method of embodiment 24 wherein the other subjects are age and sex matched with the patient.

26. The method of embodiment 24 wherein the other subjects are weight matched.

27. The method of embodiment 21 wherein the knowledge is obtained from information derived from the same subject.

28. The method of embodiment 21 wherein the information is cartilage thickness, cartilage curvature, cartilage contour or cartilage shape in a contralateral joint.

29. The method of embodiment 21 wherein the information is cartilage thickness, cartilage curvature, cartilage contour or cartilage shape in the same joint.

30. The method of embodiment 21 wherein the knowledge is curvature, contour or shape of at least one bone in the same joint.

31. The method of embodiment 30 wherein the bone is subchondral bone.

32. The method of embodiment 31 wherein the curvature, the contour or the shape of the subchondral bone is used to estimate the curvature, contour or shape of the overlying articular cartilage.

33. The method of embodiment 21 wherein the image is an image of the knee joint.

34. The method of embodiment 33 wherein the joint has arthritis.

35. The method of embodiment 34 wherein the arthritis has caused cartilage loss.

36. The method of embodiment 32 wherein the curvature, the contour or the shape of the subchondral bone is used to estimate the curvature, contour or shape of the overlying articular cartilage at the interface of the subchondral bone with the overlying articular cartilage.

37. The method of embodiment 32 wherein the curvature, the contour or the shape of the subchondral bone is used to estimate the curvature, contour or shape of the overlying articular cartilage at the external, articular surface.

38. A method of manipulating a medical image which method comprises

a. determining the gray value of a pixel on the left side of a boundary element

b. determining the gray value of a pixel on the right side of a boundary element

c. determining the distance of a boundary element to the inner cartilage surface (ICS)

whereby the inner cartilage surface is located in the joint of a human and whereby determining the distance of the boundary element to the inner cartilage surface (ICS) improves the accuracy of the manipulation.

39. The method of embodiment 38 wherein the image is an MRI and the method is used to locate the outer cartilage surface.

40. The method of embodiment 39 wherein the cartilage is normal.

41. The method of embodiment 39 wherein the cartilage is diseased.

42. The method of embodiment 38 wherein the manipulation includes a live wire algorithm.

43. The method of embodiment 42 wherein the live wire algorithm uses a cost function that employs a modified hyperbolic function that increases from 0 to 1 when the distance from the inner cartilage surface to the outer cartilage surface increases above a reference value in the femoral condyles.

44. The method of embodiment 42 wherein the live wire algorithm uses a cost function that employs a modified hyperbolic function that increases from 0 to 1 when the distance from the inner cartilage surface to the outer cartilage surface increases above a reference value in the tibial plateau.

45. The method of embodiment 42 wherein the live wire algorithm uses a cost function that employs a modified hyperbolic function that increases from 0 to 1 when the distance from the inner cartilage surface to the outer cartilage surface increases above a reference value in the patella.

46. The method of embodiment 38 wherein the manipulation includes a snake algorithm.

47. A method of manipulating an image which method comprises

a. determining the gray value of a pixel on the left side of a boundary element

b. determining the gray value of a pixel on the right side of a boundary element

c. determining the distance of the closest boundary element in the previously manipulated image slice,

whereby determining the distance of the closest boundary element in the previously manipulated image slice improves the accuracy of the manipulation.

48. The method of embodiment 47 wherein the image is an MRI and the method is used to locate the bone cartilage interface.

49. The method of embodiment 47 wherein the image is an MRI and the method is used to locate the external cartilage surface.

50. The method of embodiments 48 and 49 wherein the cartilage is normal.

51. The method of embodiments 48 and 49 wherein the cartilage is diseased.

52. A method for assessing the condition of cartilage in a joint of a human, which method comprises

(a) electronically transferring an electronically-generated image of a cartilage of the joint from a transferring device to a receiving device located distant from the transferring device;

(b) receiving the transferred image at the distant location;

(c) extracting the cartilage from the transferred image

(d) converting the transferred image to a normal or degeneration pattern of the cartilage; and

(e) transmitting the normal or the degeneration pattern to a site for analysis.

53. The method of embodiment 52 wherein the normal or the degeneration pattern is stored in a database.

54. The method of embodiment 53 wherein the database can be used to facilitate the extraction of the cartilage from the transferred images in other patients.

55. The method of embodiment 53 wherein the database contains information on subjects' age, sex, race, weight or medical condition.

56. The method of embodiment 52 wherein after step (e), the degeneration pattern is displayed as a three-dimensional image.

57. The method of embodiment 56 wherein the joint is a knee joint.

58. The method of embodiment 52, 56 or 57 wherein all steps are carried out at an initial time (T1) and are carried out again at a later time (T2).

59. The method of embodiment 58 wherein the assessment includes an analysis of the degree of degeneration of the cartilage between T1 and T2.

60. The method of embodiment 52 wherein the electronically-generated image of a cartilage is obtained by a magnetic resonance imaging (MRI) technique.

61. A method of embodiment 60, wherein the MRI technique provides a biochemical description of the cartilage.

62. A method of embodiment 60, wherein the MRI technique provides a volumetric description of the cartilage.

63. The method of embodiment 60 wherein the MRI technique results in a three-dimensional image of the cartilage.

64. The method of embodiment 63 wherein the MRI technique first obtains a series of two-dimensional views of the joint, which are then mathematically integrated to give a three-dimensional image.

65. The method of embodiment 60 wherein the MRI technique employs a gradient echo, spin echo, fast-spin echo, driven equilibrium fourier transform, or spoiled gradient echo technique.

66. The method of embodiment 60, wherein the assessment of the condition of cartilage in a joint of a human is followed by one or more assessments of the condition of the same cartilage at a later point in time.

67. A method for assessing the condition of cartilage in a joint of a human, which method comprises

(a) extracting the cartilage from an electronically-generated medical image

(b) electronically transferring the electronically-generated image of a cartilage of the joint from a transferring device to a receiving device located distant from the transferring device;

(c) receiving the transferred image at the distant location;

(d) converting the transferred image to a normal or degeneration pattern of the cartilage; and

(e) transmitting the normal or the degeneration pattern to a site for analysis.

68. The method of embodiment 67 wherein the normal or the degeneration pattern is stored in a database.

69. The method of embodiment 68 wherein the database can be used to facilitate the extraction of the cartilage from the transferred images in other patients.

70. The method of embodiment 68 wherein the database contains information on subjects' age, sex, race, weight or medical condition.

71. The method of embodiment 67 wherein after step (e), the degeneration pattern is displayed as a three-dimensional image.

72. The method of embodiment 67 wherein the joint is a knee joint.

73. The method of embodiment 67, 71 or 72 wherein all steps are carried out at an initial time (T1) and are carried out again at a later time (T2).

74. The method of embodiment 73 wherein the assessment includes an analysis of the degree of degeneration of the cartilage between T1 and T2.

75. The method of embodiment 67 wherein the electronically-generated image of a cartilage is obtained by a magnetic resonance imaging (MRI) technique.

76. A method of embodiment 75, wherein the MRI technique provides a biochemical description of the cartilage.

77. A method of embodiment 75, wherein the MRI technique provides a volumetric description of the cartilage.

78. The method of embodiment 75 wherein the MRI technique results in a three-dimensional image of the cartilage.

79. The method of embodiment 78 wherein the MRI technique first obtains a series of two-dimensional views of the joint, which are then mathematically integrated to give a three-dimensional image.

80. The method of embodiment 75 wherein the MRI technique employs a gradient echo, spin echo, fast-spin echo, driven equilibrium fourier transform, or spoiled gradient echo technique.

81. The method of embodiment 75, wherein the assessment of the condition of cartilage in a joint of a human is followed by one or more assessments of the condition of the same cartilage at a later point in time.

Detailed Specific Example

METHODS

Image Segmentation

The live wire algorithm finds the contours of an object by evaluation of a set of features for each boundary element. A boundary element (*bel*) is the oriented edge between two pixels (see Figure 4). Using an individual cost function for each feature, the feature values are converted into cost values between 0 and 1. Finally, the weighted sum of all feature costs results in a single joint cost value between 0 and 1 for each bel *b* that expresses the likelihood of *b* being part of the cartilage boundary [6]. This determines whether the pixels on either side of the bel are assigned to one tissue or the other that form the boundary. To determine the contour of a cartilage object, the user chooses a starting pixel P with a mouse click. Subsequently, the system calculates the bel path with the least sum of costs from each image pixel to *P* using a dynamic programming scheme. When the user moves the mouse cursor, the system can now display the calculated path from the current mouse position to *P* in real time. The current path can be frozen as part of the cartilage contour by the user. Thus, the cartilage contour in each slice is assembled from a number of frozen live wire segments.

The live wire contour should be drawn around the cartilage in a consistent direction. In the following it is assumed that the direction has been chosen by the user such that the cartilage is always to the right of a bel. We are currently using the following boundary element features and cost functions:

1. *Grayvalue of pixel p:* The grayvalue of pixel p (see Figure 4), which is supposed to lie outside the cartilage, is mapped to a cost value using an inverted Gaussian

function with the mean and standard deviation as parameters that have to be chosen appropriately. Grayvalues close to the mean are converted to low cost values.

2. *Grayvalue of pixel q:* The same process is applied to pixel q, which is assumed to be a cartilage pixel. These features attract the contour to pixels with grayvalues close the chosen means.

3. *Magnitude of the graylevel gradient across b* is computed according to equation 2. The cost function is a thresholding function that is 0 inside and 1 outside a given interval. This prevents the contour from locking onto the cartilage-bone interface of the tibia when segmenting the femoral outer cartilage surface.

$$f = \frac{1}{2}\left|g(p) + \frac{1}{2}g(t) + \frac{1}{2}g(v) - g(q) - \frac{1}{2}g(u) - \frac{1}{2}g(w)\right| \quad (1)$$

4. *Distance of b to closest bel in previously segmented slice:* The contour is drawn towards a previously segmented contour in an adjacent slice. Thus, one carefully segmented slice can provide useful information for subsequent slices.
The distance is calculated by means of a fast Euclidean distance transform (EDT) algorithm [12]. The cost increases linearly with the distance.

5. *Distance of outer cartilage surface (OCS) to inner cartilage surface (ICS):* Prior knowledge that femoral cartilage, for example, typically does not exceed a thickness of approximately 4 mm [7] is incorporated as another feature. If the cartilage-bone interface (ICS) is segmented first in a slice, which can usually be easily done in sagittal MR images due to high contrast between bone and cartilage, this information is helpful in regions of low contrast between OCS and surrounding tissue.
For distance calculation the same EDT algorithm as in feature 4 is used. The cost is calculated with a modified hyperbolic function that increases from 0 to 1 above 4mm. This feature prevents the OCS contour from moving too far away from the ICS contour.

6. *Direction of graylevel gradient of OCS compared with the gradient of the corresponding section of ICS:* Except in the periphery of the cartilage where the ICS and the OCS meet and in regions of defective cartilage the OCS is usually approximately parallel to the ICS. This knowledge is used to combine magnitude and direction of the graylevel gradient in order to help finding the contour in regions

of low contrast between the OCS and surrounding tissue. The lower the gradient magnitude across a bel b on the OCS, the more weight is given to its direction. The cost for b increases with increasing deviation of the direction of its gradient $\vec{\beta}$ from the direction of the gradient $\vec{\gamma}$ on the opposing ICS. A high degree of parallelism between $\vec{\beta}$ and $\vec{\gamma}$ results in a high probability of b being included in the contour. In effect, this means that the ICS is taken as a template for the OCS where the OCS is not clearly recognizable, In areas of high contrast between the OCS and surrounding tissue, however, this is not necessary, so that the gradient direction can be weighted less. This also makes the detection of cartilage defects possible.

To facilitate the selection of the Gaussian cost function parameters for the user, the images may be first processed with a Kuwahara smoothing filter with a 3x3 window size [13]. This non-linear filter reduces noise while preserving eges in the image.

Interobserver Reproducibility

In preliminary experiments interobserver reproducibility of the proposed method was assessed using sagittal MR images of the knee acquired from five. patients with different stages of osteoarthritis (1.5T GE Signa, fat-saturated 3D SPGR, TE 5ms, TR 60ms, flip angle 40°, voxel size 1.5x0.47x0.47mm^3). Three observers segmented the femoral cartilage with the live wire method, using features 1-3. Parameters measured from segmented data were total cartilage volume, maximum thickness, average thickness, and number of voxels on the OCS. Thickness values were calculated using a 3-dimensional EDT [8, 12]. Interreader reproducibility was determined as the coefficient of variation (CV%) between the three, observers for each patient.

Results

An example of the processing steps for the cartilage segmentation is given above. The contours of normal cartilage and areas of thinning and full thickness loss are correctly identified with the live wire technique

The results of the interobserver reproducibility assessment are presented in Table 1.

Table 1

Interobserver reproducibility (CV%). The average interobserver reproducibility is given as root mean square (RMS) of the CV%.

Patient	Volume	Max. thickness	Avg. thickness	Surface voxels
A	4.7%	0.2%	3.8%	1.5%
B	13.5%	7.6%	10.5%	2.7%
C	8.6%	3.3%	6.7%	0.7%
D	7.7%	4.9%	5.7%	3.1%
E	5.9%	0.7%	5.8%	1.0%
RMS	8.6%	4.3%	6.9%	2.0%

Discussion

The experiments on the interobserver reproducibility of segmentation of osteoarthritic femoral cartilage using the proposed live wire technique yielded approximately the same results as published for similar parameters obtained from healthy volunteers with the B-spline snake method [11]. However, as Table 1 also shows, the variation of values obtained for the total cartilage volume remains high. This is partially caused by difficulties to identify the correct cartilage boundaries in the peripheral regions of the femoral condyles where the sagittal imaging plane is nearly tangential to the cartilage surface, thus blurring the edges due to high partial volume effects.

In general, the live wire segmentation technique proved to provide the necessary flexibility for segmentation of osteoarthritic cartilage. New features can easily be implemented and included into the system. Subjectively, the technique greatly facilitates segmentation compared to manual delineation of the contours. Its principal advantage lies in the evaluation of local image features in a global context, which is important for the correct treatment of cartilage irregularities in segmentation.

Further improvements can be made by including methods for automatic determination of the cost function parameters from the images, which will additionally increase reproducibility. Thus, the present technique holds the potential to improve and facilitate semi-automatic segmentation of both normal and diseased cartilage.

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B-spline snakes and manual segmentation. *Magn Reson Imaging*, 17(7):1033-1042, 1999.

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The present invention is related to and can be used in combination with other inventions arising out of investigations in the laboratories of the present inventors, as well as in combination with many other independently developed or publically available techniques for the investigation and manipulation of digital images, particularly such images as they relate to medical images and the segmentation of tissues. Examples of applications related to the present invention that were developed in the laboratories of the present inventors can be found in the disclosures of the following patent documents:

PCT Publication No. WO 00/35346, published 22 June, 2000, entitled "Assessing the Condition of a Joint and Preventing Damage."

U.S. application serial No. 60/232,639, filed 14 September 2000, entitled "New Techniques for Manipulating Medical Images."

U.S. application serial No. 60/232,637, entitled "Assessing the Condition of a Joint and Assessing Cartilage Loss."

U.S. application serial No. 09/662,224, entitled "Assessing the Condition of a Joint and Devising Treatment."

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

We claim:

1. A method of assessing a digital image to determine a boundary between first and second image components, which comprises:

(a) selecting a first boundary element between two pixels being evaluated for assignment to the first or second image component;

(b) determining a first value of a first pixel on one side of the first boundary element;

(c) determining a second value of a second pixel on the other side of the first boundary element;

(d) comparing the first and second value to determine magnitude of a gradient across the first boundary element and assigning a gradient boundary value to the first boundary element;

(e) determining relative locations of (1) the first boundary element and (2) a reference element selected from the group consisting of (2a) a reference boundary element previously assigned as separating a pixel assigned to the first image component from a pixel assigned to the second image component and (2b) a reference second-boundary element previously assigned as separating a pixel assigned to one of the first and second image components from a third image component, the second-boundary element having a known, statistically significant distance or angle relationship relative to an actual boundary between real components represented by the first and second image components, and assigning a location boundary value to the first boundary element based on distance or angle of the relative locations from each other;

(f) mathematically combining the gradient boundary value and the location boundary value to provide a first potential boundary value for the first boundary element;

repeating steps (a)-(f) for a second boundary element to obtain a second potential boundary value; and

(g) assigning the first boundary element or the second boundary element as dividing the first image component from the second image component, depending on relative potential boundary values of the first and second boundary elements.

2. The method of claim 1, wherein said image is a magnetic resonance image, an ultrasound image, or an X-ray image and said method is used to locate a bone/cartilage interface or an external cartilage surface.

3. The method of claim 2, wherein said cartilage is diseased or damaged.

4. The method of claim 1, wherein said method assigns said boundary element to said first or second image component using existing knowledge of probable shape of said first or second image component.

5. The method of claim 4, wherein said digital image is of a living subject and said first and second image components comprise first and second tissues of said living subject.

6. The method of claim 5, wherein said knowledge is obtained from (a) information derived from same-type tissue images of other subjects or (b) information derived from a different image obtained from said living subject or from a different region of said tissue image.

7. The method of claim 6, wherein said other subjects are age and sex matched or weight matched with said living subject.

8. The method of claim 6, wherein said information is (a) cartilage thickness, cartilage curvature or cartilage shape in a contralateral joint or in a different region of a first joint whose image is being assessed or (b) curvature or shape of a bone in said first joint.

9. The method of claim 8, wherein said bone is subchondral bone.

10. The method of claim 9, wherein curvature or shape of the subchondral bone is used to estimate curvature or shape of overlying articular cartilage.

11. The method of claim 1, wherein said method is used to assess condition of cartilage in a joint of a human, which method further comprises:

(a) electronically transferring an electronically generated image of a cartilage of the joint from a transferring device to a receiving device located distant from the transferring device;

(b) receiving the transferred image at the distant location;

(c) extracting said cartilage from said transferred image using the method of claim 1;

(d) converting the transferred image to a normal or degeneration pattern of the cartilage; and

(e) transmitting said normal or said degeneration pattern to a site for analysis.

12. The method of claim 11, wherein said normal or said degeneration pattern is stored in a database.

13. The method of claim 1, wherein all steps are carried out at an initial time T1 and are carried out again at a later time T2.

14. The method of claim 13, wherein the assessment includes an analysis of the degree of degeneration of the cartilage between T1 and T2.

15. The method of Claim 1, wherein said digital image of a cartilage is obtained by a magnetic resonance imaging (MRI) technique.

Figure 1

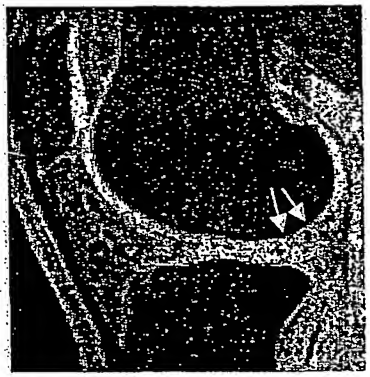


Fig. 2

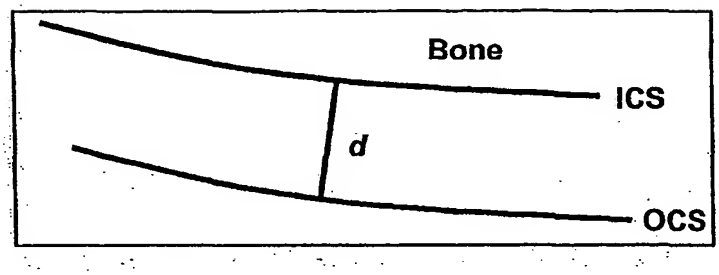
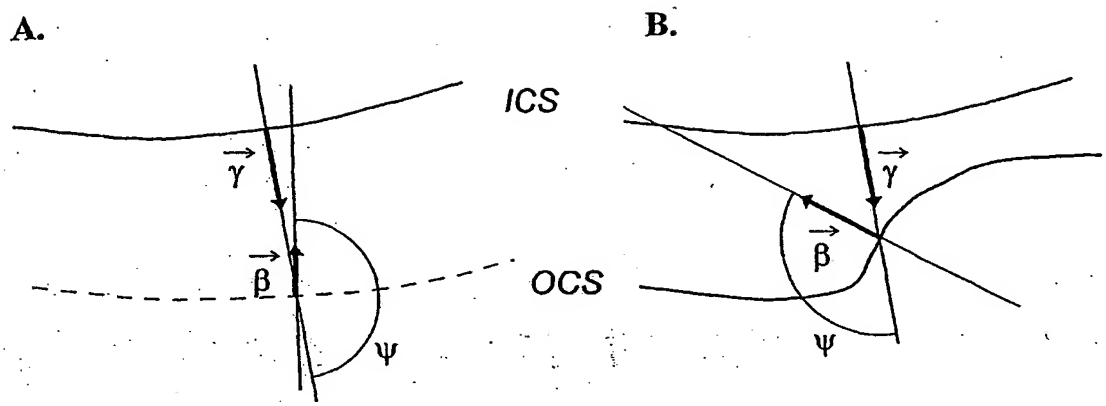


Fig. 3



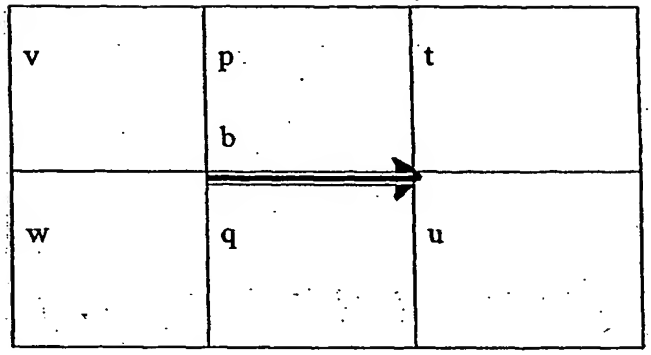


Figure 4

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(74) Agents: NEELEY, Richard, L.; Cooley Godward LLP, Five Palo Alto Square, 3000 El Camino Real, Palo Alto, CA 94306-2155 et al. (US).

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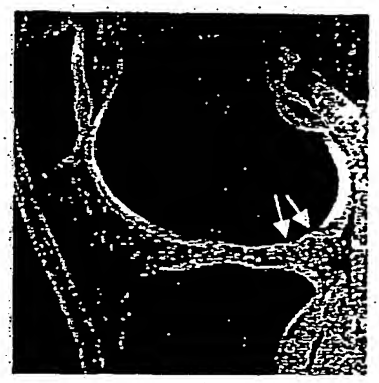
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TECHNIQUE FOR MANIPULATING MEDICAL IMAGES



(57) Abstract: The invention and the embodiments described in this invention provide new techniques for manipulating digital images and is particularly useful for extracting tissues (i.e., assigning tissue boundary locations) from medical images. These techniques can be applied to diagnosing arthritis and for monitoring disease progression or response to therapeutic intervention. The invention provides for means to extract the articular cartilage from medical images for analysis purposes.

WO 02/023483 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/42155

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G06T

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STAMMBERGER T ET AL: "Determination of 3D cartilage thickness data from MR imaging: computational method and reproducibility in the living" MAGNETIC RESONANCE IN MEDICINE, ACADEMIC PRESS, DULUTH, MN, US, vol. 41, no. 3, March 1999 (1999-03), pages 529-536, XP002161461 ISSN: 0740-3194 cited in the application abstract page 530, paragraphs MATERIALS,AND,METHODS -/-	1-15

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZOHARA A. COHEN ET AL.: "Knee cartilage topography, thickness, and contact areas from MRI: in-vitro calibration and in-vivo measurements" OSTEOARTHRITIS AND CARTILAGE, 'Online! vol. 7, 1999, pages 95-109, XP002216548 Retrieved from the Internet: <URL:http://citeseer.nj.nec.com/477079.htm l> 'retrieved on 2002-10-11! abstract page 97, left-hand column, line 8 -right-hand column, line 21	1-15
A	ANDRIACCHI THOMAS P ET AL: "Methods for evaluating the progression of osteoarthritis" JOURNAL OF REHABILITATION RESEARCH AND DEVELOPMENT, THE SERVICE, WASHINGTON, DC, US, vol. 37, no. 2, March 2000 (2000-03), pages 163-170, XP002188111 ISSN: 0748-7711 page 167, left-hand column, line 45 - line' 55	1-15
A	HONGYI LI ET AL: "A boundary optimisation algorithm for delineating brain objects from CT-scans" NUCLEAR SCIENCE SYMPOSIUM AND MEDICAL IMAGING CONFERENCE, 1993., 1993 IEEE CONFERENCE RECORD. SAN FRANCISCO, CA, USA 31 OCT.-6 NOV. 1993, NEW YORK, NY, USA,IEEE, 31 October 1993 (1993-10-31), pages 1553-1557, XP010119366 ISBN: 0-7803-1487-5 page 1553, paragraph II page 1554, paragraph III	1-15